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(57) Abstract

High capacity drug reservoirs are provided for incorporation into transdermal drug delivery systems. The drug reservoirs are comprised of a superabsorbent material, typically a cross-linked polymer, which is capable of absorbing an amount of drug formulation corresponding to at least 15 grams formulation per gram of material. Methods for making and using transdermal systems containing such reservoirs are provided as well.

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HIGH CAPACITY, SUPERABSORBENT DRUG RESERVOIRS FOR USE IN TRANSDERMAL DRUG DELIVERY SYSTEMS

Technical Field

This invention relates generally to transdermal drug delivery, and more particularly relates to high capacity, superabsorbent drug reservoirs for incorporation into transdermal drug delivery systems. The invention further relates to transdermal drug delivery systems containing the high capacity reservoirs, and to methods for manufacturing and using the new transdermal systems.

Background

The delivery of drugs through the skin provides many advantages; primarily, such a means of delivery is a comfortable, convenient and noninvasive way of administering drugs. The variable rates of absorption and metabolism encountered in oral treatment are avoided, and other inherent inconveniences -- e.g., gastrointestinal irritation and the like -- are eliminated as well. Transdermal drug delivery also makes possible a high degree of control over blood concentrations of any particular drug.

Skin is a structurally complex, relatively thick membrane. Molecules moving from the environment into and through intact skin must first penetrate the stratum corneum. They must then penetrate the viable epidermis, the papillary dermis, and the capillary

walls into the blood stream or lymph channels. To be so absorbed, molecules must overcome a different resistance to penetration in each type of tissue. Transport across the skin membrane is thus a complex phenomenon. However, it is the cells of the stratum corneum which present the primary barrier to absorption of topical compositions or transdermally administered drugs. The stratum corneum is a thin layer of dense, highly keratinized cells approximately 10-15 microns thick over most of the body. It is believed to be the high degree of keratinization within these cells as well as their dense packing which creates in most cases a substantially impermeable barrier to drug penetration.

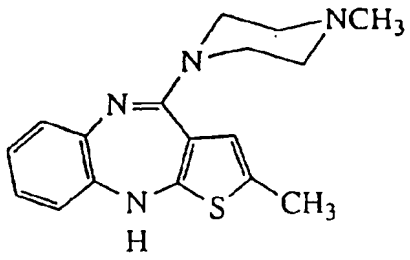
Relatively recent advances in transdermal drug delivery have enabled effective administration of a variety of drugs through the skin. These advances include the development of a number of skin penetration enhancing agents, or "permeation enhancers," to increase skin permeability, as well as non-chemical modes for facilitating transdermal delivery, e.g., the use of iontophoresis, electroporation or ultrasound. Nevertheless, the number of drugs that can be safely and effectively administered through the skin, without concomitant problems such as irritation or sensitization, remains limited.

None of the art of which applicants are aware describes transdermal drug delivery using high capacity drug reservoirs or methods for manufacturing transdermal systems containing such reservoirs. The high capacity drug reservoirs useful in conjunction with the present methods and transdermal systems are comprised of superabsorbent materials, usually crosslinked polymers which are capable of absorbing far more than their own weight. Using such materials,

the transdermal system as a whole contains a far greater quantity of drug than possible with conventional transdermal systems. This in turn enables delivery of greater quantities of drug, at higher fluxes.

The high capacity drug reservoirs may reduce or in some cases eliminate the need for permeation enhancers, which, as well known in the art, can cause irritation, sensitization, or other problems. Further, smaller transdermal patches may be made using such technology, i.e., patches that are at least as effective as prior patches in terms of overall drug release and drug flux, but are significantly reduced in terms of size.

The invention may be used to deliver a wide variety of drugs. For example, the present drug delivery systems may be used in the transdermal administration of 2-methyl-10-(4-methyl-1-piperazinyl)-4H-thieno[2,3-b][1,5]benzodiazepine, also known as "olanzapine." The drug is described in U.S. Patent No. 5,229,382 to Chakrabarti et al., issued July 20, 1993, and assigned to Lilly Industries Limited.



Olanzapine

Olanzapine is an antagonist of dopamine at the D-1 and D-2 receptors, and in addition has antimuscarinic

anticholinergic properties and antagonist activity at 5HT-2 receptor sites and at noradrenergic α-receptors (Moore et al., *J. Pharmacol. Exp. Ther.* 262(2):545-551 (1992)). The drug has relaxant, anxiolytic and anti-emetic properties, and, as explained in the Chakrabarti et al. patent, is useful in the treatment of psychosis, acute mania and mild anxiety states, and is particularly useful in the treatment of schizophrenia and schizophreniform illnesses.

Currently, olanzapine is administered orally or by injection. While the drug has been established as an effective antipsychotic agent, drug non-compliance is a serious problem, and is believed to account for approximately one-third of all short-stay hospital costs. Transdermal administration of olanzapine or a pharmaceutically acceptable salt thereof, significantly enhances patient compliance by providing an advanced delivery system useful for administering the drug over an approximately three- to seven-day period. There are a number of other advantages to administering olanzapine transdermally as well: gastrointestinal and other side effects associated with oral administration are substantially avoided; continuous delivery provides for sustained blood levels; the transdermal patch is easily removable if any side effects do occur; and the likelihood of patient acceptance is significantly improved. In general, steady-state, transdermal delivery of the drug seems to provide a far better side effect profile overall than is associated with oral administration.

The present systems are also useful in the transdermal administration of steroid drugs, including androgenic agents. Particular compounds of interest are testosterone and pharmaceutically acceptable esters and derivatives thereof. Such agents are

useful in a variety of applications, e.g., in treating hypogonadism, hypopituitarism, Addison's disease, impotence, male infertility disorders, anemia, and in male hormone replacement therapy. The invention also involves the transdermal administration of androgenic agents in combination with estrogens, in treating, for example, menopause, osteoporosis, or other conditions for which estrogen-androgen combination therapy is indicated.

Transdermal delivery of androgens, alone or in combination with estrogenic agents, has been described. *See, e.g.*, U.S. Patent No. 4,704,282 to Campbell et al., U.S. Patent No. 4,867,982 to Campbell et al., U.S. Patent No. 5,094,857 to Luderschmidt, U.S. Patent No. 5,152,997 to Ebert et al., U.S. Patent No. 5,460,820 to Ebert et al., and PCT Publication No. WO95/03764. In contrast to prior systems for administering these drugs transdermally, however, the present invention is directed to transdermal systems in which the androgenic agent is contained within drug reservoirs into which a far greater quantity of drug may be loaded than possible with conventional transdermal systems. As explained above, such systems provide a number of advantages, including delivery of greater quantities of drug, at higher fluxes, reduction of patch size, and the like.

Disclosure of the Invention

Accordingly, it is a primary object of the present invention to provide a high capacity, superabsorbent drug reservoir for transdermal administration of a drug formulation contained therein.

It is another object of the invention to provide a transdermal drug delivery system containing a high capacity, superabsorbent drug reservoir.

It is still another object of the invention to provide a method for making such a drug delivery system.

It is a further object of the invention to provide a method for administering a drug to an individual using the novel reservoirs and transdermal drug delivery systems containing them.

Additional objects, advantages and novel features of the invention will be set forth in part in the description which follows, and in part will become apparent to those skilled in the art upon examination of the following, or may be learned by practice of the invention.

The present invention is thus directed in part to high capacity, "superabsorbent" reservoirs useful in transdermal drug delivery systems, which, by virtue of the novel reservoirs, are able to deliver greater quantities of drug, at higher fluxes, than possible with conventional transdermal systems. The superabsorbent reservoirs may also reduce or in some cases eliminate the need for permeation enhancers. For those drugs which do still require the presence of an enhancer to achieve high flux, the superabsorbent reservoir provides a means whereby augmented loading of both drug and enhancer may be achieved.

Transdermal drug delivery systems containing the novel reservoirs will generally be in the form of a laminated composite comprising: (a) a backing layer; (b) the drug reservoir; and (c) a means for affixing the composite to the skin, typically either an "in-line" contact adhesive in the form of a layer underlying the entire surface of the system, or a peripheral adhesive ring. The backing layer serves as the upper surface of the system during use and is substantially impermeable to the drug. During storage

and prior to use, a release liner is present to protect the basal surface of the system.

Additional materials and components may also be present. For example, in some cases, it may be preferable or necessary to incorporate a rate-controlling membrane into the transdermal system. One or more additional reservoir and/or adhesive layers may also be included. Also, during storage and prior to use, a release liner should be present to protect the basal surface of the system.

The invention is also directed to a method for preparing a transdermal drug delivery system having a superabsorbent drug reservoir, comprising: (a) providing a superabsorbent material in the form of a substantially planar layer to serve as the drug reservoir, the layer having first and second opposing surfaces; (b) absorbing drug formulation into the drug reservoir; (c) laminating to the first surface of the reservoir a backing layer that is substantially impermeable to the drug and which defines the upper surface of the system during use; and (d) laminating to the opposing second surface of the reservoir a pressure-sensitive, pharmaceutically acceptable adhesive layer comprised of a material that is permeable to the drug.

The invention further provides a method for transdermally administering a drug to a mammalian individual, comprising positioning topically on the individual a transdermal drug delivery system containing a high capacity drug reservoir of a superabsorbent material as provided herein.

The systems are useful, for example, in the transdermal administration of androgenic agents such as testosterone. Administration is conducted for a time period and at an administration rate effective to provide the necessary therapy, e.g., treatment of

impotence, infertility disorders, or the like. Using high capacity, polyurethane hydrogel reservoirs, transdermal patches on the order of 30 cm^2 or smaller may be used to deliver the selected androgenic agent, while still achieving a drug flux that is for all contemplated indications more than sufficient. Optimally, the androgenic agent patches are designed to be worn for 24-hour periods.

The systems are also useful in transdermally administering olanzapine or a pharmaceutically acceptable salt thereof, to treat an individual suffering from or susceptible to psychosis, acute mania or mild anxiety states, particularly schizophrenia and schizophreniform illnesses. Transdermal administration of olanzapine is conducted for a time period and at an administration rate effective to alleviate the symptoms at issue. The preferred transdermal system used for administration of olanzapine or a pharmaceutically acceptable salt thereof is as described above, i.e., it will typically be a laminated composite comprised of a backing layer, the high capacity, polyurethane hydrogel reservoir, a means for affixing the composite to the skin, and, optionally, other membranes and components as well. The transdermal system is preferably constructed such that an effective dose of olanzapine or a pharmaceutically acceptable acid addition salt thereof will be delivered for a period in the range of about three to seven days.

Brief Description of the Drawings

FIG. 1 illustrates in schematic form one embodiment of a superabsorbent drug reservoir-type transdermal delivery system which may manufactured so as to contain a superabsorbent drug reservoir as provided herein.

FIG. 2 is a graph illustrating the olanzapine skin flux from a system comprising a maleic anhydride-isobutylene copolymer superabsorbent material, as explained in Example 1.

FIG. 3 is a graph illustrating the olanzapine skin flux from a system comprising a maleic anhydride-isobutylene copolymer superabsorbent material and a drug permeation rate-controlling membrane.

FIG. 4 represents in graph form the testosterone flux profiles from the superabsorbent systems of the invention as evaluated in Example 4.

FIG. 5 represents in graph form the cumulative permeation of testosterone using the superabsorbent systems of the invention, also as evaluated in Example 4.

Modes for Carrying Out the Invention

Before describing the present invention in detail, it is to be understood that this invention is not limited to particular transdermal drug delivery system configurations, particular drug/vehicle formulations, or the like, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

It must be noted that, as used in this specification and the appended claims, the singular forms "a", "an" and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to "a permeation enhancer" includes a mixture of two or more permeation enhancers, reference to "an excipient" or "a vehicle" includes mixtures of excipients or vehicles, reference

to "an adhesive layer" includes reference to two or more such layers, and the like.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by those of ordinary skill in the art to which the invention pertains. Although any methods and materials similar or equivalent to those described herein can be used in the practice for testing of the present invention, the preferred materials and methods are described herein.

In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below.

By "transdermal" delivery, applicants intend to include both transdermal (or "percutaneous") and transmucosal administration, i.e., delivery by passage of a drug through the skin or mucosal tissue and into the bloodstream. The term "body surface" will sometimes be used herein to refer to either the skin or the mucosal tissue.

By a "high capacity" drug reservoir, as used herein, is meant a drug reservoir containing a quantity of drug or drug formulation which is greater than that which is typically possible using conventional manufacturing techniques or transdermal drug delivery systems.

By a "superabsorbent" material, as used herein, is intended a material capable of absorbing or adsorbing an amount of fluid corresponding to more than 15 grams, preferably more than 25 grams, most preferably more than 50 grams, per gram of superabsorbent material. Superabsorbent materials are known that are capable of absorbing or adsorbing 300 to 1000 times their weight in fluids as well. Such superabsorbent materials not only absorb fluids but also are able to retain the fluid that has been

absorbed, while remaining generally insoluble in the fluid absorbed. As will be explained below, the superabsorbent materials are typically crosslinked polymers, which may be either homopolymers or copolymers.

By an "effective" amount of a drug is meant a nontoxic but sufficient amount of the drug to provide the desired therapeutic or prophylactic effect. With respect to olanzapine, for example, an "effective" amount of drug refers to that dose of drug which will be effective in relieving or preventing symptoms of psychosis, acute mania, mild anxiety, or the like. An "effective" amount of a permeation enhancer as used herein means an amount that will provide the desired increase in skin permeability and, correspondingly, the desired depth of penetration, rate of administration, and amount of drug delivered.

By "predetermined area of skin" is intended a defined area of intact unbroken living skin or mucosal tissue. That area will usually be in the range of about 5 cm^2 to about 150 cm^2, more usually in the range of about 5 cm^2 to about 100 cm^2, and preferably in the range of about 5 cm^2 to about 60 cm^2. However, it will be appreciated by those skilled in the art of transdermal drug delivery that the area of skin or mucosal tissue through which drug is administered may vary significantly, depending on patch configuration, dose, and the like. Also, as noted above, the present technology enables preparation of generally smaller patches, typically in the range of about 5 cm^2 to about 20 cm^2.

"Penetration enhancement" or "permeation enhancement" as used herein relates to an increase in the permeability of skin to a pharmacologically active agent, i.e., so as to increase the rate at which the

drug permeates through the skin and enters the bloodstream. The enhanced permeation effected through the use of such enhancers can be observed by measuring the rate of diffusion of drug through animal or human skin using a diffusion cell apparatus as described in the Examples herein.

"Carriers" or "vehicles" as used herein refer to carrier materials suitable for transdermal drug administration, and include any such materials known in the art, e.g., any liquid, gel, solvent, liquid diluent, solubilizer, or the like, which is nontoxic and which does not interact with other components of the composition in a deleterious manner. Examples of suitable carriers for use herein include water, silicone, liquid sugars, waxes, petroleum jelly, and a variety of other materials. The term "carrier" or "vehicle" as used herein may also refer to stabilizers, crystallization inhibitors, or other types of additives useful for facilitating transdermal drug delivery.

By the term "saturated," as used in conjunction with the transdermal delivery of androgenic agents, is meant a pharmaceutical formulation in which the drug is present at saturation; when the present systems are used for the administration of an androgenic agent, the drug is present in the pharmaceutical formulation contained in the drug reservoir at or above saturation.

When transdermal administration of "olanzapine" *per se* is indicated herein, it is to be understood that the described method, formulation or system extends to pharmaceutically acceptable acid addition salts as well.

The high capacity drug reservoirs of the invention are comprised of a superabsorbent material and a drug formulation. The nature of the

superabsorbent material is not critical. Typically, crosslinked polymer (including copolymer) compositions are preferred, such as poly(acrylates), poly(maleic anhydrides), poly(vinyl alcohols), poly(ethylene oxides), poly(hydroxy methylenes), polysaccharides, and the like, as described in Chen et al. (1985) *Synthetic and Natural Polymers*, in Chatterjee (Ed.) *Absorbency*, chapter VI, pp. 197-216 (Elsevier, Amsterdam). Specific examples of superabsorbent materials include, but are not limited to: the reaction product at elevated temperature and pressure of hydrolyzed starch polyacrylonitrile graft copolymer, optionally having added thereto a polyhydric alcohol such as glycerol (*see*, U.S. Patent Nos. 4,467,012 and 4,412,036 to Pedersen et al.); a polymer network of a crosslinked polyurethane prepared from an isocyanate-terminated poly(oxyalkylene)polyol and a substantially linear addition polymer containing functional groups selected from the group consisting of carbamoyl, substituted carbamoyl and carboxy, and the alkali metal and ammonium salts thereof (such polymers are described, for example, in U.S. Patent No. 4,731,391 to Garvey); a skeletal network of a cellular polymeric foam, preferably a polyurethane, containing a superabsorbent material such as carboxymethyl cellulose, starch-grafted sodium polyacrylate or sodium polyacrylate (as described, for example, in U.S. Patent No. 4,985,467 to Kelly et al.); and a superabsorbent crosslinked ampholytic ion pair copolymer, for example, the ammonium cation 3-methacrylamidopropyltrimethylammonium and a sulfonate anion such as sulfonate, 2-methylacryloyloxyethane sulfonate, vinyl sulfonate, styrene sulfonate, or the like, as disclosed in U.S. Patent No. 5,216,098 to Ahmed et al. Other suitable superabsorbent materials, which may be obtained commercially or synthesized

using known techniques, may be used as well, as will be appreciated by those of ordinary skill in the art. Preferably, the superabsorbent material is an olefin/alkyl carboxylate copolymer such as a maleic anhydride-isobutylene copolymer, as may be obtained from Camelot Superabsorbents Incorporated (Charlotte, NC) as Fiberdri® superabsorbent fibers. A superabsorbent film comprising such a copolymer may be obtained from Concert Industries Limited (Thurso, Quebec, Canada).

Turning now to an exemplary transdermal drug delivery system containing drug reservoirs comprised of a superabsorbent material, reference may be had first of all to FIG. 1. The drug delivery system is in the form of a laminated composite, generally designated as **10**, and comprises a backing layer **11**, a superabsorbent reservoir layer **12** containing drug **12a** absorbed by a superabsorbent material **12b**, a contact adhesive **13** and a release liner **14**. The rate-controlling membrane **15** interposed between drug reservoir layer **12** and contact adhesive **13** is optional.

The backing layer **11** functions as the primary structural element of the system and provides the system with much of its flexibility, drape and, preferably, occlusivity. The material used for the backing layer should be inert and incapable of absorbing drug, enhancer or other components of the pharmaceutical composition contained within the system. The backing is preferably made of one or more sheets or films of a flexible elastomeric material that serves as a protective covering to prevent loss of drug and/or vehicle via transmission through the upper surface of the system, and will preferably impart a degree of occlusivity to the system, such that the area of the skin covered on application

becomes hydrated. The material used for the backing layer should permit the system to follow the contours of the skin and be worn comfortably on areas of skin such as at joints or other points of flexure, that are normally subjected to mechanical strain with little or no likelihood of the system disengaging from the skin due to differences in the flexibility or resiliency of the skin and the system. Examples of materials useful for the backing layer are polyesters, polyethylene, polypropylene, polyurethanes and polyether amides. The layer is preferably in the range of about 15 microns to about 250 microns in thickness, and may, if desired, be pigmented, metallized, or provided with a matte finish suitable for writing.

Drug reservoir layer **12** provides a means for containing drug **12a**, and is comprised of a superabsorbent material **12b**. The reservoir layer will generally although not necessarily range in thickness from about 1 to about 100 mils, preferably about 25 to 60 mils. It will be appreciated that the thickness of the reservoir will depend on a variety of considerations, including the quantity of drug to be incorporated in the reservoir, desired patch size, and the like.

A pharmaceutically acceptable contact adhesive layer **13** functions to secure the system to the skin during use. In an alternate embodiment, a peripheral ring of contact adhesive is provided on the basal surface of the system. The contact adhesive material is a pressure-sensitive adhesive suitable for long-term skin contact, and is also physically and chemically compatible with the drug formulation, i.e., the drug itself and any carriers and vehicles employed. Preferred materials for this layer include polysiloxanes, polyisobutylenes, polyacrylates, polyurethanes, plasticized ethylene-vinyl acetate

copolymers, low molecular weight polyether amide block polymers (e.g., PEBAX), tacky rubbers such as polyisobutene, polystyrene-isoprene copolymers, polystyrene-butadiene copolymers, and mixtures thereof.

To protect the basal surface of the system during storage and just prior to use, a release liner 14 is provided to cover the adhesive layer. The release liner is a disposable element which serves solely to protect the system prior to application. Typically, the release liner is formed from a material which is impermeable to the drug, vehicle and adhesive, and easily stripped from the contact adhesive. Release liners are typically treated with silicone or fluorocarbons; an example of an optimal material is silicone-coated polyester.

Any number of drugs may be delivered transdermally using the reservoirs and drug delivery systems of the invention, i.e., any compound suitable for transdermal or transmucosal administration which induces a desired systemic or local effect. Such substances include the broad classes of compounds normally delivered through body surfaces and membranes, including skin. In general, this includes: anti-infectives such as antibiotics and antiviral agents; analgesics and analgesic combinations; anorexics; antihelminthics; antiarthritics; antiasthmatic agents; anticonvulsants; antidepressants; antidiabetic agents; antidiarrheals; antihistamines; antiinflammatory agents; antimigraine preparations; antinauseants; antineoplastics; antiparkinsonism drugs; antipruritics; antipsychotics; antipyretics; antispasmodics; anticholinergics; sympathomimetics; xanthine derivatives; cardiovascular preparations including calcium channel blockers and beta-blockers such as pindolol and antiarrhythmics;

antihypertensives; diuretics; vasodilators including general coronary, peripheral and cerebral; central nervous system stimulants; cough and cold preparations, including decongestants; hormones such as estradiol and other steroids, including corticosteroids; hypnotics; immunosuppressives; muscle relaxants; parasympatholytics; psychostimulants; sedatives; and tranquilizers. The amount of active agent incorporated into the drug reservoir will vary, depending on the agent, the intended dosage, the individual undergoing treatment, the particular indication, and the like.

It is important to note that the present invention enables transdermal delivery of drugs which typically display low skin flux, as the quantity of drug which may be loaded into the high capacity drug reservoir is significantly greater than with conventional systems. Other preferred drugs are those that require high flux to achieve a desired therapeutic effect and thus may require the presence of an enhancer in the drug formulation. The present invention provides a drug reservoir comprising a superabsorbent material that, for the same size patch, is capable of absorbing not only more drug than prior patches but is also capable of absorbing more enhancer as well.

Steroids represent one class of drugs with which the present reservoirs and transdermal systems are particularly useful. Examples of steroid drugs which may be administered in conjunction with the invention include: progestogens such as flurogestone acetate, hydroxyprogesterone, hydroxyprogesterone acetate, hydroxyprogesterone caproate, medroxyprogesterone acetate, norethindrone, norethindrone acetate, norethisterone, norethynodrel, desogestrel, 3-keto desogestrel, gestadene and

levonorgestrel; estrogens such as estradiol and its esters (e.g., estradiol benzoate, valerate, cypionate, decanoate and acetate), ethynyl estradiol, estriol, estrone and mestranol; and corticosteroids such as betamethasone, betamethasone acetate, cortisone, hydrocortisone, hydrocortisone acetate, corticosterone, fluocinolone acetonide, prednisolone, prednisone and triamcinolone.

Also, in one specific embodiment of the invention, the present transdermal systems are used to administer androgenic agents such as the naturally occurring androgens androsterone and testosterone; pharmaceutically acceptable esters of testosterone, typically esters formed from the hydroxyl group present at C-17, and particularly the enanthate, propionate, cypionate and phenylacetate esters; and pharmaceutically acceptable derivatives of testosterone such as methyltestosterone, testolactone, oxymetholone and fluoxymesterone. Testosterone and the 17-esters thereof, particularly the enanthate, propionate and cypionate esters, are preferred. Such agents are useful in a variety of applications, e.g., in male hormone therapy, in treating hypogonadism, hypopituitarism, Addison's disease, impotence, male infertility disorders, anemia, and the like. Other pharmaceutically active agents, particularly additional steroidal agents, may be administered along with the selected androgenic agent. These agents will generally be estrogens and/or progestogens. The amount of each such additional agent incorporated into the drug reservoir will vary, depending on the intended dosage. Normally, the daily dosage of estrogenic agent will be at least about 0.03 mg/day, while the daily dosage of progestogen will be at least about 0.2 mg/day, depending, of course, on the particular estrogen and progestogen to be

administered. Administration of an androgenic agent in combination with an estrogen and/or a progestogen is useful, for example, in the treatment of menopausal symptoms, osteoporosis, or other conditions for which such combination therapy is indicated.

When the present invention is used in conjunction with the delivery of androgenic agents, administration is conducted for a time period and at an administration rate effective to provide the necessary therapy, e.g., treatment of impotence, infertility disorders, or the like. The agent should be delivered at a dosage of at least about 3 mg/day, more preferably at least about 6 mg/day. Transdermal patches on the order of 30 cm^2 or smaller may be used to deliver the selected androgenic agent, while still achieving a drug flux that is for all contemplated indications more than sufficient. Generally, a flux of at least about 100, more preferably at least about 200 $\mu g/cm^2/day$, is necessary. The present drug reservoirs achieve such fluxes. Optimally, the androgenic agent patches are designed to be worn for 24-hour periods.

While not essential, it is preferred that transdermal administration of androgenic agents be conducted at or above saturation. That is, the androgenic agent is present at or above saturation with respect to its concentration in the formulation contained in the drug reservoir.

The reservoirs and transdermal systems of the invention are also useful in the transdermal administration of olanzapine. The specific method and drug delivery system for delivering olanzapine transdermally may vary, but necessarily involve application of a drug delivery system containing olanzapine or a pharmaceutically acceptable acid addition salt thereof to a predetermined area of the

skin or mucosal tissue at an administration rate and for a period of time sufficient to provide an effective blood level of drug for a desired period of time. The drug is present in a high capacity, superabsorbent drug reservoir within a transdermal delivery system such as the exemplary system described above. It should be noted that this embodiment of the invention, while primarily directed to the treatment of individuals suffering from or susceptible to psychosis, acute mania or mild anxiety states, may extend to any use of olanzapine deriving from its activity an antagonist of dopamine at the D-1 and D-2 receptors, its antimuscarinic anti-cholinergic properties, and/or its antagonist activity at 5HT-2 receptor sites and noradrenergic α-receptors. The transdermal olanzapine system formulated using the novel reservoirs are preferably constructed so that an effective dose of olanzapine or a pharmaceutically acceptable salt thereof will be delivered for a period in the range of about three to seven days.

Olanzapine or any other basic drug may be administered in the form of the base or as a pharmaceutically acceptable acid addition salt. As will be appreciated by those skilled in the art, the base form of the drug can be converted to an acid addition salt by treatment with a stoichiometric excess of a selected acid. Such acid addition salts may be formed, for example, with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, or with organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, hydroxymaleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-

toluenesulfonic acid, naphthalene-2-sulfonic acid, salicylic acid and the like.

Similarly, acidic drugs may be administered in the acid form or, as will be appreciated by those skilled in the art, as a pharmaceutically basic salt. The salts may be derived from inorganic bases, e.g., the ammonium, potassium, sodium, calcium and magnesium salts. Alternatively, the salts may be derived from pharmaceutically acceptable nontoxic bases, including isopropylamine, trimethylamine, dimethylamine, triethylamine, ethanolamine, dicyclohexylamine, choline, tromethylamine, and the like.

The high capacity reservoirs of the invention may in some cases eliminate the need for a permeation enhancer. However, enhancers may still be preferred or even required for administering certain drugs, e.g., steroids, including androgenic agents, and olanzapine. Suitable enhancers include, but are not limited to, dimethylsulfoxide (DMSO), dimethyl formamide (DMF), N,N-dimethylacetamide (DMA), decylmethylsulfoxide (C_{10}MSO), polyethylene glycol monolaurate (PEGML), propylene glycol (PG), propylene glycol monolaurate (PGML), glycerol monolaurate (GML), methyl laurate (ML), lauryl lactate (LL), methyl decanoate (MD), isopropyl myristate (IPM), terpenes such as menthone, C_2-C_6 alkanediols, particularly 1,2-butanediol and 1,3-butanediol (1,2-BD and 1,3-BD), lecithin, the 1-substituted azacycloheptan-2-ones, particularly 1-n-dodecyl-cyclazacycloheptan-2-one (available under the trademark Azone® from Whitby Research Incorporated, Richmond, VA), alcohols, and the like. Vegetable oil permeation enhancers, as described in commonly assigned U.S. Patent No. 5,229,130 to Sharma, may also be used. Such oils include, for example, safflower oil, cotton seed oil and corn oil.

Preferred enhancers for use in conjunction with the present invention, and particularly in the transdermal administration of androgenic agents and olanzapine, are esters given by the formula $[CH_3(CH_2)_mCOO]_nR$ in which m is an integer in the range of 8 to 16, n is 1 or 2, and R is a lower alkyl (C_1-C_3) residue that is either unsubstituted or substituted with one or two hydroxyl groups. In the preferred embodiment herein, the ester component is a lower alkyl (C_1-C_3) laurate (i.e., m is 10 and n is 1), and in a particularly preferred case is "PGML." It will be appreciated by those skilled in the art that the commercially available material sold as "PGML" is typically a mixture of propylene glycol monolaurate itself, propylene glycol dilaurate, and either propylene glycol, methyl laurate, or both. Thus, the terms "PGML" or "propylene glycol monolaurate" as used herein are intended to encompass both the pure compound as well as the mixture that is typically obtained commercially.

Also preferred are fatty acids and fatty alcohols corresponding to the above-defined fatty esters. Thus, fatty acids useful as permeation enhancers herein will generally have the formula $CH_3(CH_2)_mCOOH$, where m is as above, while the fatty alcohols will have the formula $CH_3(CH_2)_mCH_2OH$.

Other preferred enhancers are wherein a fatty ester as described above is combined with an ether component selected from the group consisting of diethylene glycol monoethyl ether and diethylene glycol monomethylether. Such enhancer compositions are described in detail in U.S. Patent Nos. 5,053,227 and 5,059,426 to Chiang et al., both of common assignment herewith.

Particularly preferred permeation enhancers are selected from the group consisting of C_2-C_6 alkanediols, fatty esters having the structural formula $[CH_3(CH_2)_mCOO]_nR$, fatty acids having the structural formula $CH_3(CH_2)_mCOOH$, fatty alcohols having the structural formula $CH_3(CH_2)_mCH_2OH$, and mixtures thereof, where m and n are as defined above. It has been found that ternary vehicle combinations in which such a fatty alcohol or acid is combined with a fatty ester and a C_2-C_6 alkanediol, e.g., 1,2-butanediol, 1,3-butanediol, and the like, are particularly effective enhancer compositions for use in conjunction with the present invention.

If an enhancer is used, the type and amount of enhancer will similarly depend on a number of factors, e.g., the strength of the particular enhancer, the desired increase in skin permeability, rate of administration, and amount of drug delivered.

The drug formulations contained in the high capacity reservoirs may also include standard carriers or vehicles useful for facilitating drug delivery, e.g., stabilizers, antioxidants, anti-irritants and crystallization inhibitors.

Preferred drug formulations, i.e., the drug-containing composition which is loaded into the drug reservoir, will typically contain on the order of about 0.1 wt.% to 20 wt.%, preferably about 1 wt.% to 10 wt.% drug, with the remainder of the formulation representing other components such as enhancers, vehicles or the like. If enhancers are present, they will generally represent on the order of approximately 1 wt.% to 25 wt.% of the drug formulation.

The superabsorbent reservoir is prepared by dissolving the drug in water or other suitable solvent, incorporating any desired carriers, vehicles,

enhancers or the like in the solution, and contacting the superabsorbent material with the drug solution to permit absorption thereof. The drug solution may be applied to the superabsorbent material by any conventional method such as by dipping, coating, spraying or printing; a suitable method for "printing" drug formulation on the superabsorbent material is disclosed in U.S. Patent No. 4,915,950 to Miranda et al. This drug-containing reservoir may then be incorporated into a transdermal drug delivery system in the form of a laminated composite, using any number of techniques. For example, the superabsorbent drug reservoir may be laminated to the selected backing layer and subsequently laminated to a contact adhesive layer.

Alternatively, a transdermal system containing a superabsorbent reservoir may be prepared as follows by first casting a selected contact adhesive material, present in solution, onto a release liner. Solvent is evaporated therefrom, and the adhesive is then laminated to the superabsorbent drug reservoir, which is in turn transfer-laminated onto the backing film. Other suitable manufacturing techniques may be used as well, as will be appreciated by those working in the field of transdermal drug delivery.

It may be desirable to include a rate-controlling membrane between the superabsorbent reservoir and a contact adhesive layer, when present. Representative materials useful for forming rate-controlling membranes include polyolefins such as polyethylene and polypropylene, polyamides, polyesters, ethylene-ethacrylate copolymer, ethylene-vinyl acetate copolymer, ethylene-vinyl methylacetate copolymer, ethylene-vinyl ethylacetate copolymer, ethylene-vinyl propylacetate copolymer, polyisoprene,

polyacrylonitrile, ethylene-propylene copolymer, and the like. Generally, a preferred material useful to form the rate-controlling membrane is ethylene-vinyl acetate copolymer. The particular material selected will be such that the flux of drug component or of one or more non-drug components, i.e., will be controlled as desired.

It is to be understood that while the invention has been described in conjunction with the preferred specific embodiments thereof, that the description above as well as the examples which follow are intended to illustrate and not limit the scope of the invention. Other aspects, advantages and modifications within the scope of the invention will be apparent to those skilled in the art to which the invention pertains.

In the following examples, efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental error and deviation should be accounted for. Unless indicated otherwise, temperature is in degrees C and pressure is at or near atmospheric.

Experimental

Materials: Olanzapine free base was provided by Eli Lilly. Testosterone was purchased from Sigma Chemical Company and used as received. All chemicals used were of reagent grade.

Preparation of Transdermal Systems: Drug was dissolved in selected vehicle combinations as indicated in the Examples below. A superabsorbent material was absorbed with a combination of liquid

vehicles and cut into disks which were then applied to the skin.

Assay methodology: For evaluation of skin flux, samples were analyzed by HPLC using UV-detection at 265 nm and 220 nm. Chromatographic resolution was achieved using a Brownlee RP-18 column, 100 mm x 4.6 mm, with a 5 μm particle size (for olanzapine), and a Zobrax C_8 column, 250 mm x 4.6 mm, also with a 5 μm particle size (for testosterone), run at a flow rate of 1.5 ml per min (olanzapine) or 1.0 ml per minute (testosterone) at ambient temperature. The mobile phase was a mixture of 47%-48% acetonitrile: 52%-53% water. The retention time for olanzapine was about 3.0 min; the retention time for testosterone was about 4.0 min.

In Vitro Skin Permeation of Drug:

Skin Preparation: Human cadaver skin was used for the permeation studies. The frozen skins were thawed and the epidermal layers (stratum corneum and viable epidermis) were separated from the full-thickness skin by immersing it in water at 60°C for two min. This epidermis was either used immediately for flux studies or stored at -20°C for later studies.

Skin permeation from prototypes: Modified Franz cells were used for evaluating the prototype systems for delivery of drug. Prototype systems, prepared as described above, were placed on top of the epidermis. Gentle pressure was applied to ensure full contact between the prototype and the stratum corneum. The skin membrane with the prototype system was then mounted carefully between the donor and the receiver compartments. The receiver compartment was filled with 7.5 ml of pH 7.4 buffer and the temperature was maintained at 32°C ± 1°C throughout the experimental period. The entire receiver content was withdrawn and

replaced with fresh buffer. Samples were assayed by HPLC.

Data Analysis: Skin flux ($\mu g/cm^2/hr$) was determined at each time point by dividing the amount of drug penetrating the skin during that period of time corrected for the surface area by the duration of time.

Example 1

Olanzapine base was dissolved in a combination of vehicles as indicated in Table 1 and absorbed onto a highly absorbent maleic anhydride-isobutylene polymeric film obtained from Concert Industries Limited (Thurso, Quebec, Canada). The systems were cut into 1.25 cm^2 circles and applied to human cadaver skin using a Franz diffusion cell. At 8, 24, 48, 70 and 96 hours, the entirety of the receiver fluid was replaced with fresh fluid and analyzed for olanzapine using HPLC method. The formulations are listed in Table 1 and the results are shown in FIG. 2.

Table 1

Formulation	
1.	Saturated olanzapine in vehicle of 10% lauric acid + 45% methyl laurate + 45% 1,2-butanediol adsorbed on two pieces 1.25 cm^2 each of superabsorbent film (Concert 100136 #95068)
2.	Saturated olanzapine in vehicle of 10% oleyl alcohol + 45% PGML + 45% 1,2-butanediol adsorbed on two pieces 1.25 cm^2 each of superabsorbent film (Concert 100136 #95068)
3.	Saturated olanzapine in vehicle of 10% oleic acid + 45% methyl caprate + 45% 1,2-butanediol adsorbed on two pieces 1.25 cm^2 each of superabsorbent film (Concert 100136 #95068)

The data summarized in graph form in FIG. 2 indicate that effective skin fluxes of olanzapine can be achieved from superabsorbent materials using different vehicles.

Example 2

Olanzapine base was dissolved in a combination of vehicles as indicated in Table 2 and absorbed onto a highly absorbent polymeric film as in Example 1. At the same time, an ethylene-vinyl acetate ("EVA") membrane was cut into 2 cm^2 circles and mounted onto the skin. Following this procedure, the polymeric film having drug absorbed thereon was applied and the procedure of Example 1 was followed. The formulations are listed in Table 2 and the results are shown in FIG. 3.

Table 2

Formulation	
1.	olanzapine saturated in 10% lauric acid + 45% methyl laurate + 45% 1,2-butanediol and absorbed on superabsorbent film (Concert 100136 #95068) with EVA 19%, 4 mil membrane.
2.	olanzapine saturated in 10% oleic acid + 45% methyl caprate + 45% 1,2-butanediol and absorbed on superabsorbent film (Concert 100136 #95068) with EVA 19%, 4 mil membrane.

The data obtained show that the flux of drug from the superabsorbent material can be regulated using a rate-controlling membrane.

Example 3

A skin flux study was conducted to evaluate the flux of testosterone from superabsorbent systems.

Testosterone was dissolved in a combination of vehicles as indicated in Table 3 and absorbed on a

highly absorbent polymeric film, with and without an associated "rate-controlling" EVA membrane (as in Examples 1 and 2, respectively). The superabsorbent material containing testosterone was then applied to the skin as 1/2 inch diameter disks. The formulations evaluated are listed in Table 4; the platforms were evaluated with respect to both skin flux and cumulative permeation. The flux of testosterone from the superabsorbent platforms exhibited the desired phasic profiles. With a ternary vehicle and superabsorbent design, the testosterone delivered at 24 hr was about 250 $\mu g/cm^2$. The results are also illustrated graphically in FIGS. 4 and 5.

Table 3
Cumulative Permeation of Testosterone from Platforms at 24 Hours

Formulation #	Platform	Om ($\mu g/cm^2$)
1.	Superabsorbent (lauric acid:ML:BD 20:40:40)	249±47
2.	Superabsorbent (lauryl alcohol:ML:BD 20:40:40)	150±9
3.	Superabsorbent (benzyl alcohol:MD:BD 20:40:40)	162±11

Claims:

1. A drug reservoir for use in a transdermal drug delivery system, comprising a layer of a superabsorbent material having a drug formulation absorbed therein.

2. The drug reservoir of claim 1, wherein the superabsorbent material is a crosslinked polymer capable of absorbing an amount of drug formulation corresponding to more than 15 grams drug formulation per gram of superabsorbent material.

3. The drug reservoir of claim 1, wherein the superabsorbent material is selected from the group consisting of poly(acrylates), poly(maleic anhydrides), poly(vinyl alcohols), poly(ethylene oxides), poly(hydroxy methylenes), polysaccharides and olefin/alkyl carboxylate copolymers.

4. The drug reservoir of claim 3, wherein the superabsorbent material comprises an olefin/alkyl carboxylate copolymer.

5. The drug reservoir of claim 4, wherein the superabsorbent material comprises a maleic anhydride-isobutylene copolymer.

6. The drug reservoir of claim 1, wherein the drug is a steroid drug.

7. The drug reservoir of claim 1, wherein the drug formulation further comprises a permeation enhancer.

8. A transdermal drug delivery system for administering a drug to a predetermined area of a body surface, comprising a laminated composite of:

(a) a reservoir layer comprised of a superabsorbent material and having a drug formulation absorbed therein;

(b) a means for affixing the composite to the body surface during drug administration; and

(c) a backing layer that is substantially impermeable to the drug and which defines the upper surface of the system during use.

9. The system of claim 8, wherein the superabsorbent material is a crosslinked polymer capable of absorbing an amount of drug formulation corresponding to more than 15 grams drug formulation per gram of superabsorbent material.

10. The transdermal delivery system of claim 8, wherein the superabsorbent material is selected from the group consisting of poly(acrylates), poly(maleic anhydrides), poly(vinyl alcohols), poly(ethylene oxides), poly(hydroxy methylenes), polysaccharides and olefin/alkyl carboxylate copolymers.

11. The system of claim 10, wherein the superabsorbent material comprises an olefin/alkyl carboxylate copolymer.

12. The system of claim 11, wherein the superabsorbent material comprises a maleic anhydride-isobutylene copolymer.

13. A method for making a transdermal drug delivery system for administering a drug to a

predetermined area of the body surface, wherein said system includes a superabsorbent drug reservoir, comprising:

(a) providing a superabsorbent material in the form of a substantially planar layer to serve as the drug reservoir, the drug reservoir having first and second opposing surfaces;

(b) absorbing drug formulation into the drug reservoir;

(c) laminating to the first surface of the drug reservoir a backing layer that is substantially impermeable to the drug and serves to define the upper surface of the system during use; and

(d) laminating to the opposing second surface of the drug reservoir a pressure-sensitive, pharmaceutically acceptable adhesive layer comprised of a material that is permeable to the drug.

14. A method for transdermally administering a drug to a mammalian individual, comprising positioning topically on the individual a transdermal drug delivery system containing the drug reservoir of claim 1.

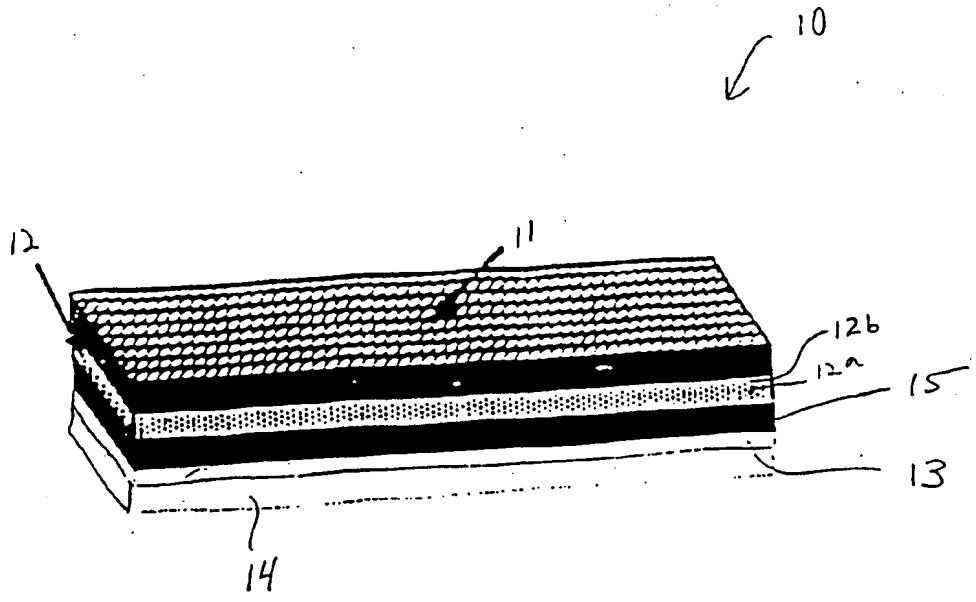


FIG. 1

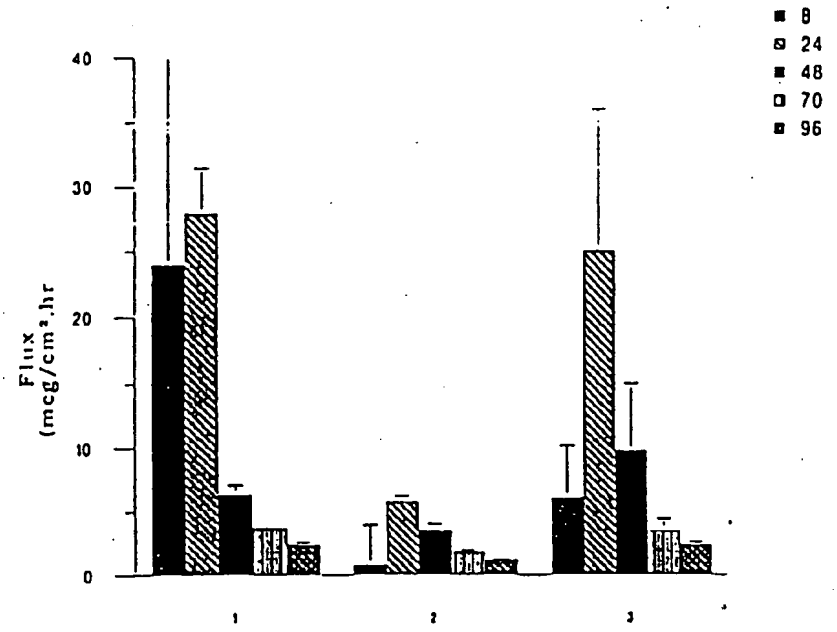


FIG. 2

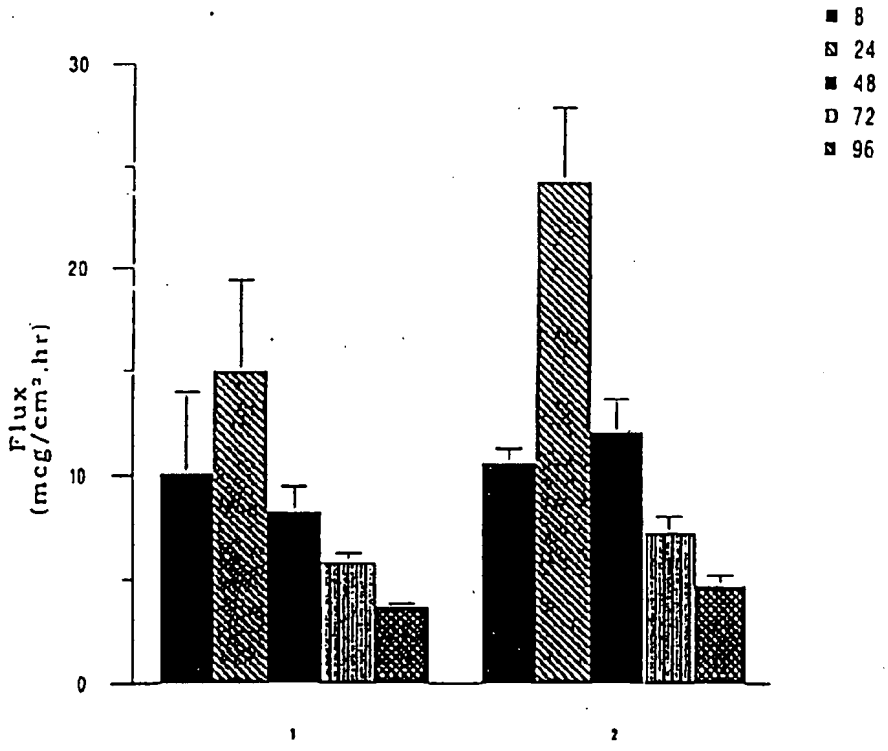
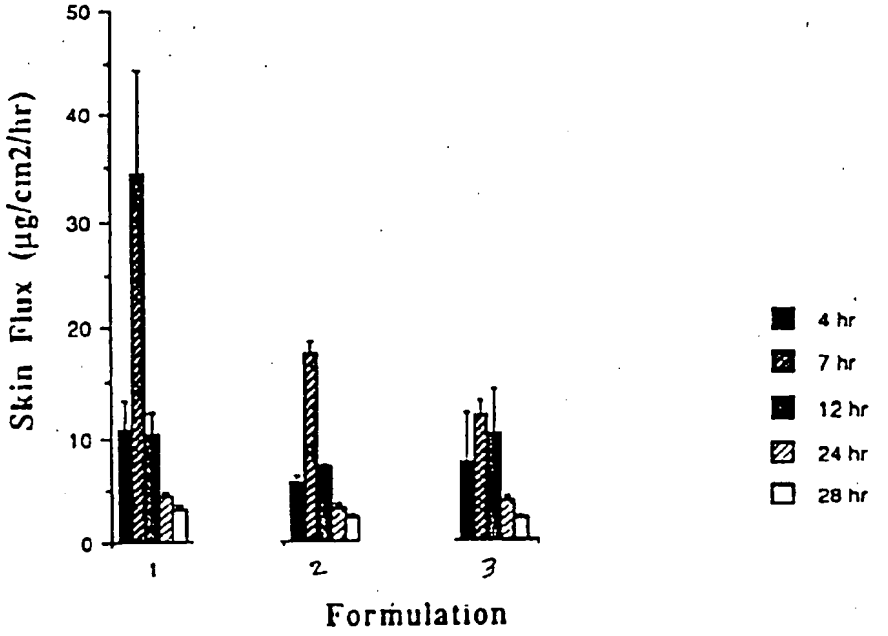


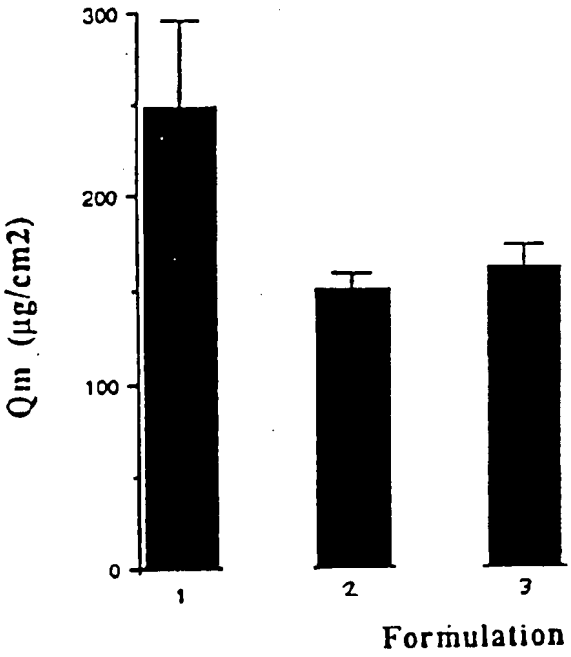
FIG. 3

Figure 4
Skin Flux Profiles of Testosterone from Various Platforms



Formulation #	Platform
1.	Superabsorbent (Lauric Acid:ML:BD 20:40:40)
2.	Superabsorbent (Lauryl Alcohol:ML:BD 20:40:40)
3.	Superabsorbent (Benzyl Alcohol:MD:BD 20:40:40)

Figure 5
Cumulative Permeation of Testosterone at 24 Hours



Formulation #	Platform
1.	Superabsorbent (Lauric Acid:ML:BD 20:40:40)
2.	Superabsorbent (Lauryl Alcohol:ML:BD 20:40:40)
3.	Superabsorbent (Benzyl Alcohol:MD:BD 20:40:40)